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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,242	06/20/2003	Phillip Dan Cook	ISIS-5213	6684
32650	7590	02/22/2006	EXAMINER	
WOODCOCK WASHBURN LLP ONE LIBERTY PLACE - 46TH FLOOR PHILADELPHIA, PA 19103			EPPS FORD, JANET L	
			ART UNIT	PAPER NUMBER
			1633	
DATE MAILED: 02/22/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/601,242

Applicant(s)

COOK ET AL.

Examiner

Janet L. Epps-Ford

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 November 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 44,47 and 49-68 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44,47 and 49-68 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

1. The Declaration under 37 CFR 1.132 filed 11-21-05 is insufficient to overcome the rejection of claims 44, 47 and 49-68 based upon 35 USC § 112, 1st paragraph, lack of enablement as set forth in the last Office action because: Applicant's comments regarding antisense therapy and the references cited in the Declaration are not commensurate in scope with the claimed invention, the references cited in the Declaration are based upon experimental data established after the filing date of the instant application. The instant claims are drawn to the treatment of any disease in any organism comprising the administration of an antisense compound of unknown length and comprising an exponential number of potential modification combinations based upon the variations in nucleobase and nucleoside compositions encompassed by the instant claims. Due to the unpredictability associated with antisense based therapeutics as described in the prior Office action (Crooke (1998), Branch (1998) and Jen (2000)), and as set forth below, the experimental data set forth in the references cited by Applicant are not considered to be representative of the full scope of the claimed invention which is drawn to the generic treatment of any disease comprising the administration of antisense compounds according to the present invention.

2. Although Applicants cite multiple references suggesting that antisense therapy works, the examiner agrees that in certain instances, and with specific antisense constructs and targets that certain antisense effects have been produced with the production of certain specific therapeutic effects. However, these observations have

been produced after an enormous amount of experimentation to get one particular antisense structure to work. These findings in no way can be used to suggest that antisense therapy targeting one particular gene target encoding a protein, wherein the protein is known to be associated with one particular disease state, can be easily and without undue experimentation be readily applicable to the treatment of any disease associated with the expression of one particular protein.

Response to Arguments

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 44, 47, and 49-68 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 44, 47, and 49-58 are broadly drawn to the treatment of an organism having a disease characterized by the undesired production of protein comprising contacting the organism with a compound comprising a plurality of units linked by covalent linkages in a sequence that is hybridizable to a complementary nucleic acid. The instant method broadly encompasses contacting an organism with a compound that is hybridizable to a complementary nucleic acid that is unrelated to the protein that is

associated with the disease to be treated. The claim broadly reads on the treatment of an unspecified disease comprising contacting a compound of unspecified sequence that is hybridizable to an unspecified nucleic acid.

Claims 59-68 are broadly drawn to methods of concurrently enhancing hybridization and RNase H activation in an unspecified organism comprising the step of contacting the organism in an unspecified manner with an oligonucleotide of the invention having an unspecified sequence. The instant claims broadly encompass a method of treatment since the method is to be practiced *in vivo* in an organism.

5. Applicant's arguments filed 11-21-05 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the following grounds (see page 10, paragraphs 2-3 of Applicant's response):

Those skilled in the art following the teachings provided in the specification could readily prepare oligonucleotides that possess the features recited in the claims and exhibit activity *in vivo* against targets of interest. The claims recite methods of treatment and methods for enhancing hybridization and RNase H activation that utilize oligonucleotides that have the following three features: (1) at least one of the nucleotide units of the oligonucleotide is functionalized to increase the nuclease resistance of the oligonucleotide; (2) at least one of the nucleotide units bears a substituent group that increases the binding affinity of the oligonucleotide for its target nucleic acid; and (3) a plurality of the nucleotide units have 2'-deoxy-*erythro*-pentofuranosyl sugar moieties that are consecutively located within the oligonucleotide.

The combination of these three features within a single oligonucleotide imparts unique and beneficial properties to the oligonucleotide. For example, as discussed in the accompanying declaration of C. Frank Bennett, six oligonucleotides possessing these features have been the subject of clinical trials (Bennett Decl., ¶7). Each of the six oligonucleotides is directed against a different molecular target, and has been tested clinically for the treatment of either cancer, rheumatoid arthritis, diabetes, or multiple sclerosis (*id.*).

Applicants therefore concluded (see page 10, paragraph 4):

It is thus known in the art that antisense oligonucleotides that possess the three features described above exhibit *in vivo* activity against multiple targets. As confirmed by Dr. Bennett, by following the teachings provided in the specification, those skilled in the art could readily prepare oligonucleotides possessing the three features, and those oligonucleotides would be expected to exhibit antisense activity *in vivo* against targets of interest (*id.*, ¶8). Accordingly, the specification provides sufficient disclosure to teach those skilled in the art how to practice the full scope of the presently claimed methods without undue experimentation.

Contrary to Applicant's assertions, due to the unpredictability associated with the behavior of antisense oligonucleotides in response to chemical modifications as taught by Crooke (2001), the six oligonucleotides described in paragraph 7 (based upon a publication dated 2003) of the Bennett Declaration, cannot be considered representative or predictive for the entire genus of the instant claims. Specifically, Crooke (2001), at pages 1-3, describe a variety of factors which influence the cellular behavior of oligonucleotides, including oligonucleotide structure, i.e. the presence or absence of sequences which cause the oligonucleotide to be prone to the formation of complex secondary structures, the structure of the RNA target can have a profound influence on the affinity of the oligonucleotide to its target, it was also stated that the oligonucleotide chemical class (i.e. the class of modification) influences the characteristics of uptake and well as the mechanism of uptake. It was therefore concluded by Crooke (see page 2, last paragraph, through page 3) "[G]iven the foregoing, it is obvious that conclusions about in vitro uptake must be very carefully made and generalizations are virtually impossible. Thus, before an oligonucleotide could be said to be inactive in vitro, it should be studied in several cell lines....Finally, extrapolations from in vitro uptake studies to predictions about in vivo pharmacokinetic behavior are entirely inappropriate..." Moreover, Crooke continues to describe other factors that influence the behavior of antisense oligonucleotides in a cellular environment, that prevent the skilled artisan from making predictions regarding the activity of oligonucleotide in a cellular environment, in particular Crooke mentions that protein binding can influence

cellular uptake, distribution, metabolism and excretion of antisense oligonucleotides, it may produce non-antisense effects that can be mistakenly interpreted as antisense and complicate the identification of an antisense mechanism. In addition to proteins, oligonucleotides are also known to interact with other biological molecules, such as lipids or carbohydrates, and such interactions, like those with proteins, will be influenced by the chemical class of the oligonucleotide studied, according to Crooke, "[U]nfortunately, essentially no data bearing on such interactions are currently available." Furthermore, Crooke describes the role of "terminating mechanisms," according to Crook, oligonucleotides may employ several terminating mechanisms. The dominant terminating mechanism is influenced by RNA receptor site, oligonucleotide chemical class, cell type, and probably many other factors (see section #6, page 3-4). In this section #6, Crooke further states that "[v]ariations in terminating mechanisms may result in significant changes in antisense potency and studies have shown significant variations from cell type to cell type in vitro, it is essential that the terminating mechanism be well understood..[U]nfortunately, at present, our understanding of terminating mechanisms remain rudimentary."

As set forth above the disclosure of Crooke (2001) clearly suggests that there are a significant number of factors that influence the behavior of oligonucleotides in a cellular environment. Based upon these factors, the skilled artisan would not accept on its face that the full scope of antisense oligonucleotide encompassed by the instant claims, would be useful for the treatment of any disease wherein the antisense targets a particular protein that is associated with that particular disease.

The data set forth in the teachings of Crooke (2001), which reports that antisense oligonucleotides exhibited *in vivo* activity against 49 targets when administered to five species of animals using 11 modes of administration, was not referenced, nor set forth in the specification as originally filed. Nor were the specific antisense oligonucleotides that are used in Crooke (2001) were not exemplified in the specification as filed. Moreover, the disclosure of Crooke (2001) suggests that although there has been some reported activity of antisense oligonucleotide in animal models, much of the work has not established a clear correlation between the actual antisense mechanism of action, and its corresponding effect in the animal model, it was concluded that further experimentation is required to establish this correlation (see page 22, section #2, 1st paragraph), see also the conclusion at page 26, 4th paragraph:

In conclusion, although it is of obvious importance to interpret *in vivo* activity data cautiously, and it is clearly necessary to include a range of controls and to evaluate effects on target RNA and protein levels and control RNA and protein levels directly, it is difficult to argue with the conclusion today that ***some effects have been observed in animals that are most likely primarily due to an antisense mechanism.***

This passage suggests again, that although some “effects” were observed in these animal models, it is clear that further experimentation is required to conclude with absolute certainty that these effects were directly associated with an antisense mechanism.

Moreover, the disclosure of Crooke (2001) does not provide evidence of the general applicability of antisense for the treatment of any and all diseases as suggested by Applicant’s claims, which read on generically “a method of treating an organism having a disease characterized by the undesired production of a protein comprising contacting the organism with a compound” according to the present invention.

Scherer et al. (December 2003), provides a review of the state of the art of antisense therapy after the filing date of the instant application. Scherer et al. summarizes the state of antisense technology by stating: "[T]he major classes of antisense agents currently used by investigators for sequence specific mRNA knockdowns are antisense oligonucleotides (ODNs), ribozymes, DNAzymes and RNA interference (RNAi). Whatever the method, the problems for effective application are remarkably similar: efficient delivery, enhanced stability, minimization of off-target effects and identification of sensitive sites in the target RNAs. These challenges have been in existence from the first attempts to use antisense research tools, and need to be met before any antisense molecule can be widely accepted as a therapeutic agent." (see page 1457) Scherer et al. concludes by stating: "[R]egardless of which antisense technology is applied, the challenge of ensuring specificity remains paramount because of the potential for nontargeted alteration of gene expression." The disclosure of Scherer et al. clearly suggests that the challenges associated with antisense technology, prevent the technology from being generally applicable for the treatment of any and all diseases. *It is noted that the instant claims do not require 100% complementarity to its target, this feature of the claimed invention opens up a greater possibility for binding to non-target sites.*

Applicants are relying upon the state of the art of antisense technology as of 2001 and 2003 to establish that the specification as filed, which claims a priority date of 12/24/1991 was fully enabling. The data associated with the ability of the antisense compounds set forth in Bennett (2003) was not set forth in the specification as originally

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filed back in 1991. Nor is it apparent that the experimental methods used to produce the effects associated with the oligonucleotides of Bennett were set forth in the specification as filed. As per MPEP § 2164.05(a) [R-2], a specification must be enabling as of the filing date. "Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art. The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed."

As stated previously, the successful treatment of a disease by pharmaceutical composition comprising an antisense compound was unknown in the art as of the earliest claimed priority date. The quantity of experimentation required to practice the invention as claimed would require determining the structures of the mRNA targets *in vivo*, and the structures of the modified antisense oligonucleotides, modes of delivery in a *in vivo* such that the processing of said mRNA target is inhibited at a significant level and for a sufficient amount of time to produce the desired therapeutic effect. At the time of earliest filing date, neither the specification as filed, nor the prior art, provided any specific guidelines in this regard. The deficiencies in the specification would constitute

undue experimentation since these steps must be achieved without specific instructions from the specification before one is enabled to practice the claimed invention.

In regards to the amount of direction or guidance presented, the specification as filed does not provide sufficient guidance and/or instruction that would teach one of skill in the art how to successfully treat an organism having a disease associated with the undesired production of a protein in an organism comprising contacting said organism with a compound comprising a plurality of units linked by covalent linkages in a sequence that is hybridizable to a complementary nucleic acid. The specification as filed provides only guidance for practicing methods *in vitro* (see pages 41-46), wherein said methods comprise contacting cells *in vitro* with a compound that comprises a sequence that is hybridizable to a nucleic acid that is associated with the expression of human ras. The specification as filed provides only information regarding the ability of antisense treated cells to reduce the level of human ras *in vitro* by measuring the level of human ras mRNA in antisense treated cells in comparison to a control (see procedures 1-5). The examples do not provide any direct evidence of phenotypic effects on the antisense treated cells, for example there is no indication that cell growth was inhibited. Furthermore, the instant specification does not provided any clear nexus between inhibiting human ras by antisense administration in human cells or tissues wherein said antisense resulted in the treatment or prophylaxis of a disease or condition associated with ras in said human cells or tissues.

Moreover, the level of predictability or unpredictability associated with the antisense therapeutic art at the effective filing date of the instant application was

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previously set forth in the prior Office Action. Specifically, it was established that Crooke (1998), concluded that “extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted].” The present specification provides only *in vitro* data. There is no reference to the production of any therapeutic effect comprising the administration of the compounds disclosed in the specification as filed.

It is apparent from Branch, Crooke, and Jen et al. that the art of antisense base therapeutics (at the time of filing) is unpredictable and those highly skilled in the art are working towards making the antisense therapy more predictable have many obstacles to overcome. Therefore, claims to antisense based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

Due to the limited guidance in the specification as filed, Applicant's reliance upon post-filing data, the unpredictability associated with antisense behavior in a cellular environment, and the generic nature of the claimed invention, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the delivery of antisense *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of

guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary effect (treating an organism with a disease associated with the undesired production of a protein) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 59, and 63-68 are rejected under 35 U.S.C. 102(b) as being anticipated by Sarin et al.

8. The prior art is applied to the extent that they do not read on a therapeutic method for treating a disease, but are considered to anticipate the claim invention since the applied reference teach the delivery of compounds which mete the structural limitations of the oligonucleotides recited in the claimed methods.

9. Sarin et al. discloses antisense compounds comprising an internal region of 2'deoxyerythropentofuranosyl beta nucleosides, and terminal regions comprising

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nucleosides with methylphosphonate modifications. Additionally, Sarin et al. discloses oligonucleotides having an internal region with nucleosides comprising methylphosphonate modifications, and an external region having 2'deoxyerythropentofuranosyl beta nucleosides, see Table 1, page 7450.

10. Claims 59, and 63-66 are rejected under 35 U.S.C. 102(a) as being anticipated by Saison-Behmoaras et al.

Saison-Behmoaras et al. discloses an oligodeoxyribonucleotide comprising a 5' Acridine moiety and a 3' dodecanol hydrophobic moiety. This doubly modified oligodeoxynucleotide induces RNase H cleavage activity, the 5' Acridine moiety serves to protect the oligonucleotide against exonucleases, the dodecanol moiety enhances cellular uptake, and both the acridine and the dodecanol groups function to stabilize the interaction of the oligonucleotide with its target nucleic acid (see page 1117, 1st col. Last paragraph).

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11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

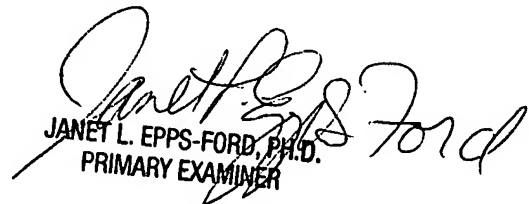
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Janet L. Epps-Ford
Primary Examiner
Art Unit 1633

JLE



JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER